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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/805,220
Filing Date: March 22, 2004
Appellant(s): YAMAGUCHI ET AL.

William J. Simmons
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed May 22, 2009 appealing from the Office action mailed September 22, 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Yamaguchi, K. *et al.*, "Synthetic peptide-based electrochemiluminescence immunoassay for anti-Borna disease virus p40 and p24 antibodies in rat and horse serum", *Annals of Clinical Biochemistry*, vol. 38 (July 2001), pp. 348-355.

Watanabe, M. *et al.*, "Antibodies to Borna Disease Virus in Infected Adult Rats: An Early Appearance of Anti-p10 Antibody and Recognition of Novel Virus-Specific

Proteins in Infected Animal Brain Cells", *Journal of Veterinary Medical Science*, vol. 62, no. 7 (2000), pp. 775-778.

Planz, O. *et al.*, "Pathogenesis of Borna Disease Virus: Granulocyte Fractions of Psychiatric Patients Harbor Infectious Virus in the Absence of Antiviral Antibodies", *Journal of Virology*, vol. 73, no. 8 (August 1999), pp. 6251-6256.

Hatalski, C. *et al.*, "Neutralizing Antibodies in Borna Disease Virus-Infected Rats", *Journal of Virology*, vol. 69, no. 2 (February 1995) pp. 741-747.

Carbone, K.M., "Borna Disease Virus and Human Disease", *Clinical Microbiology Reviews*, vol. 14, no. 3 (July 2001), pp. 513-527.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 17, 24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamaguchi *et al.* (*Ann. Clin. Biochem.* 2001, 38:348-355, "Yamaguchi"), in view of Watanabe *et al.* (*J. Vet. Med. Sci.*, 2000, 62(7):775-778, "Watanabe"), as evidenced by Planz *et al.* (*Journal of Virology*, 1999, 73:6251-6256, "Planz"), and further in view of Hatalski *et al.* (*Journal of Virology*, February 1995, 69(2):741-747, "Hatalski"), and Carbone, K.M. (*Clin. Micro. Rev.*, 2001, 14(3):513-527, "Carbone").

Yamaguchi discloses a synthetic peptide-based electrochemiluminescence immunoassay (ECLIA) for anti-BDV p40 and p24 IgG antibodies in rat and horse serum (abstract). Yamaguchi teaches the synthesis of 13 peptides having hydrophilic BDV p40 and p24 sequences that were fixed into microbeads (page 349, Table 1). Table 1, page 349, discloses a p40 peptide that is identical to Appellant's SEQ ID NO: 3 (PKRRLVDDADAMEDQDLY, line 1 of Table

1), and a p24 peptide that is identical to Appellant's SEQ ID NO: 1 (QPVDQLLKDLRKNPS, line 10 of Table 1). Rabbit anti-BDV p40 or p24 antiserum was detected by ECLIA immunoassay. ECLIA assay involves the use of an electrode and measurement of photons emitted from the secondary antibodies bound to the BDV antibody-antigen complexes (page 350, first column). The ECLIA method is an immune agglutination reaction method (antigen-antibody binding), and is a fine particle counting method (electrode-photon). Yamaguchi is silent on the use of the antigen polypeptide of p10 (SEQ ID NO: 8) and the aspect of testing for both IgM and IgG antibodies.

Watanabe discloses a study on the time course for appearance to antibodies to BDV antigens p40, p24, p18 and p10 (abstract). Watanabe found that anti-p10 antibodies (IgG) were detected in sera of BDV-infected rats as early as anti-p40 and anti-p24 antibodies (abstract). Watanabe's findings are indicated as useful for establishing diagnostic methods for BDV infection and for understanding its pathogenesis and replication (page 777, second column, last paragraph). It would have been obvious to include the detection of p10 in Yamaguchi's method. One would have been motivated to detect anti-p10 antibodies, as well as anti-p40 and anti-p24 antibodies for the purpose of increasing the sensitivity of Yamaguchi's method. Watanabe suggests that antibodies to individual viral proteins and BDV-specific antigens are useful for establishing diagnostic methods (page 777, second column, last paragraph). One would have had a reasonable expectation of success given that Watanabe found anti-p10, anti-p24 and anti-p40 antibodies in serum at the same time (abstract).

Neither Yamaguchi nor Watanabe disclose Appellant's SEQ ID NO: 8. While Watanabe discloses the use of p10, the sequence of p10 is not disclosed in the Watanabe reference.

However, the sequence of p10 includes Appellant's SEQ ID NO: 8, as evidenced by Planz's disclosure of a p10 sequence that is identical to SEQ ID NO: 8 (see Planz, page 6254, "Sequence analysis of BDV RW98", the sequence of which was submitted to EMBL AF158631, and contains the p10 sequence of BDV isolate RW98).

Hatalski discloses the detection of neutralizing antibodies to p40, p23 and gp18 in BDV-infected rats (abstract). Hatalski tested for the presence of both IgG and IgM antibodies to recombinant and native BDV proteins using electrochemiluminescence (page 741, second column, section entitled, "SDS-PAGE, Western blot and immunoprecipitation (IP)"). One would have been motivated to modify Yamaguchi's method by testing for the presence of IgM as well as IgG in order to detect infection as early as possible. Carbone discloses that the first serological evidence of virus infection is often IgM antibody. IgG appears as the immune response matures (page 516, first column, second full paragraph entitled, "Anti-BDV antibody detection"). Given that Hatalski demonstrates that IgM is present in response to BDV infection, and Carbone indicates that IgM is often the first serological evidence of BDV infection, one would have had a reasonable expectation of success that testing for the presence of IgM and IgG would have worked in Yamaguchi's method. Therefore, the invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

(10) Response to Argument

Appellant's arguments have been carefully considered but fail to persuade. Each of Appellant's arguments is addressed in turn below according to the same outlining/numbering used in the Appeal Brief.

Section A of the Appeal Brief (pages 9-12) sets forth the essential elements recited in the claims and explains how each of the cited references in the obviousness rejection lack one or more of those elements.

- Appellant asserts that the combined teachings of Watanabe, Hatalski and Carbone fail to provide the motivation to modify Yamaguchi's ECLIA method to include synthetic p10 peptides or p10 antibodies.
  - In response to Appellant's assertion that there is no motivation *in the references*, the Office is not required to provide a *reference* that suggests a motivation to combine teachings (see MPEP 2144). The Office has provided the reasoning that the addition of p10 would increase the sensitivity of Yamaguchi's method. The reasonable expectation of success comes from the fact that Watanabe found anti-p10, anti-p24 and anti-p40 antibodies in serum at the same time (Watanabe, abstract), and that Watanabe suggests that antibodies to individual viral proteins and BDV-specific antigens are useful for establishing diagnostic methods (page 777, second column, last paragraph).
  - With regard to the synthetic p10 peptides, the synthetic production of the peptides does not change the fact that the prior art's p10 peptides have the

exact same sequence as Appellant's peptides (see Planz). As for the p10 antibodies, one would have been motivated to detect anti-p10 antibodies, as well as anti-p40 and anti-p24 antibodies for the purpose of increasing the sensitivity of Yamaguchi's method.

- Appellant also asserts that the references fail to provide the motivation to examine both IgM and IgG antibodies.
  - Again, the Office is not required to provide a *reference* that suggests a motivation to combine teachings. The motivation to examine both IgM and IgG antibodies stems from the desirability of detecting infection as early as possible. Carbone discloses that the first serological evidence of virus infection is often IgM antibody. IgG appears as the immune response matures (Carbone, page 516, first column, second full paragraph entitled, "Anti-BDV antibody detection"). Given that Hatalski demonstrates that IgM is present in response to BDV infection, and Carbone indicates that IgM is often the first serological evidence of BDV infection, one would have had a reasonable expectation of success that testing for the presence of IgM and IgG would have worked in Yamaguchi's method to increase sensitivity.

Section B1 of the Appeal Brief (pages 13-16) asserts that the Office improperly relied upon hindsight conclusory statements to maintain the obviousness rejection.

- Appellant asserts that the Office's motivation for combining the teachings of Watanabe with Yamaguchi is unsupported. Specifically, Appellant argues that Watanabe contains information regarding BDV viral proteins, not the synthetic

peptides recited in Appellant's claims (SEQ ID NO: 1, 3 and 8). Appellant also points out that Watanabe fails to disclose detecting IgM and/or IgG antibodies to BDV. Appellant argues that the motivation to increase sensitivity is not present in Watanabe or Yamaguchi, and is therefore improper hindsight reconstruction by the Office.

- In response, Appellant appears to be arguing the references individually. It is acknowledged that Watanabe does not teach all the elements of the claimed invention, thus the Office has set forth an obviousness rejection. With regard to the use of synthetic versus natural peptides, there is no difference between the two given their identical sequences.
- With regard to the lack of a motivational statement in Yamaguchi and Watanabe, again, the Office is not required to provide a *reference* that suggests a motivation to combine teachings.
- With regard to hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

- Appellant further argues that the additional BDV antigen added to Yamaguchi's method might compromise the specificity of the assay unless that antigen is

carefully selected by examining its expression profile and the cross reactivity of the antibody raised against the antigen. Appellant asserts that the Office failed to challenge that the validity of a diagnostic test can be determined by measuring the rate of sensitivity and specificity, thus it is equally important to improve the specificity of diagnostic tests to minimize false positives and prevent unnecessary treatment. Appellant also points to Watanabe's statement on page 777, column 2, ("the results in this study could be worthy for establishment of diagnostics method for BDV infection") as being conjecture only. Appellant further points to several statements made in Yamaguchi regarding the difficulties in diagnosing BDV infection, which include IFA not always giving definite results, insufficient sensitivity, time lost and high cost, the latter two referring to scale-up processes of Western blots and IP analyses.

- In response to Appellant's arguments, the Office has addressed this aspect of Appellant's arguments previously in the advisory action of January 15, 2009. As to the possibility that the additional antigen added to Yamaguchi's method might compromise specificity, the ordinary artisan would be capable of determining the parameters required to successfully perform the assay with the additional antigen. Further, multiple antigen/antibody detection in the art of BDV assay is commonly practiced, evidenced by Yamaguchi and Watanabe.
- With regard to Appellant's remarks concerning the validation of assays, the Office notes that validation studies are not pertinent to the instant situation. In

the obviousness analysis, only a *reasonable expectation of success* is required. Validation studies are performed to fine-tune the assay and are not part of the process of invention of the assay.

- Further, with regard to the remarks of Watanabe and Yamaguchi that Appellant believes to cast doubt on the expectation of success of detecting BDV, these statements do not preclude the detection of BDV with IFA methods. In the obviousness analysis, only a *reasonable expectation of success* is required. Appellant has not provided any evidence as to why the detection of p10, in addition to other antigens, would be expected to result in an inoperable assay.

- Appellant argues that it is known in the art that most IgM antibodies quickly disappear, approximately one month after their appearance, and are replaced by IgG antibodies (specification, page 2, first paragraph). Appellant notes that Carbone states that it is unlikely to obtain acute phase serum in natural BDV infections (page 516, col. 1, lines 37-40).
  - In response, it is understood that IgM is replaced by IgG and that acute-phase serum is not always available in natural infection with BDV. However, the Office has reasoned that if one does not know the stage of infection, one would be motivated to increase sensitivity of Yamaguchi's assay to detect *any possible markers of an infection at any stage*, which includes IgM (for the earlier stage) and IgG (for later stages).

Section B2 of the Appeal Brief (pages 16-20) sets forth the assertion that the unpredictable art of BDV infection is improperly accorded no weight by the Office in considering patentability.

- Appellant points out several statements in the Carbone reference that discuss the unpredictability of knowing the infectious stage of BDV infection and the difficulties faced using IFA techniques. Appellant points out several statements in the Yamaguchi reference that discuss the unpredictability in diagnosis of BDV infection, and that WB and IP analyses may be more reliable and specific than IFA methods. Appellant points out statements in the Planz reference with regard to the following: "due to conflicting results obtained in attempts to detect viral nucleic acid consistently in human blood from psychiatric patients, this issue is still controversial", page 6251, col. 1., and "interestingly, in these sera, no virus specific antibodies could be detected, even at dilutions of 1:2 in immunofluorescence", page 6255, first column, first paragraph. Appellant points out that the Hatalski reference does not recognize p10 as being important in BDV infection detection, rather p18.
  - In response, the Office recognizes that the art as a whole acknowledges that the acute and persistent stages of BDV infection are difficult to determine based on antibody detection using IFA methods. However, the statements that Appellant has emphasized in their arguments are not evidence of *no expectation of success*. While there are difficulties to be addressed with specificity of the assays, these do not preclude one from detecting BDV

using IFA methods. Of course, WB analysis would be more accurate than IFA techniques, but that does not teach away from using IFA techniques. The fact that specificity in the IFA assays is not as sensitive as one would like is evidence of room for improvement, not inoperability.

- In response to Planz's teachings regarding detection of nucleic acid, the instant claims are not drawn to detection of nucleic acid. With regard to the absence of detection of antibodies in sera samples, this result in Planz relates to sera samples, whereas the claims are not limited to any particular type of sample.
- With regard to the emphasis of p18 detection in Hatalski and the non-appreciation of p10 in Hatalski, this is not evidence of non-obviousness. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). If every reference of the obviousness rejection taught every element of the claimed invention, the rejection would be one of anticipation rather than obviousness.

The Second Section B of the Appeal Brief (pages 21-24) sets forth the assertion that the Office failed to appreciate numerous teachings away from the invention.

- Appellant asserts that Yamaguchi teaches away from the combination suggested by Office because the Yamaguchi's method detects only p40 and p24. Yamaguchi states that p40 and p24 are good markers. Appellant compares the assay of Yamaguchi and the instantly claimed assay that includes detection of p10 in addition to p24 and p40. Appellant notes that in Table 1 of the specification, the detection of BDV infection was 95.7% when detecting p10, p24 and p40, as opposed to 73.9% when detecting only p24 and p40.
  - In response, the emphasis of p24 and p40 detection in Yamaguchi and the non-appreciation of p10 in Yamaguchi, is not evidence of teaching away. Note that Yamaguchi did not state that p24 and p40 were the only markers ever to be used for BDV detection.
  - Further, the increased detection of BDV in the assay that detected p10, p24 and p40 is not surprising because the sensitivity of the assay was increased. By detecting another antigen/antibody, the chances of detecting BDV are greater.
- Appellant asserts that the title of the Planz reference clearly indicates that BDV infection can be present without the presence of antibodies.
  - In response, Planz is directed to detection of nucleic acid of BDV. Planz does not teach that antibodies to BDV are never present.
- Appellant asserts that Hatalski and Carbone teach away for the same reasons as discussed above where arguments from Section B2 are rebutted.

Section C of the Appeal Brief (pages 24-26) set forth the assertion that Office failed to appreciate unexpected superior results of the claimed methods.

- Appellant asserts that it was unappreciated in the art that it requires an unusually long period of time for the class switching from IgM to IgG to occur. Appellant notes that IgM antibodies are detected even one year after BDV infection (page 12, line 17-22). Appellant argues that without this information about the long period of time for class switching, one would not have been motivated to detect both IgM and IgG at a later phase of BDV infection.
  - In response to Appellant's arguments, the Office notes that the claims are not limited to detection of BDV at later stages of infection. Since one cannot determine an active or past infection by detecting antibodies, one can only determine whether an infection has ever taken place. Thus, if one does not know the stage of infection, one would be motivated to increase sensitivity of Yamaguchi's assay to detect any possible markers of an infection at any stage, which includes IgM (for the earlier stage) and IgG (for later stages). Appellant's discovery that IgM is present one year after infection does not have any impact on the motivation to increase sensitivity of the assay because the claims are not limited to detection of BDV at any certain period of time.
- Appellant also asserts that the unexpected and superior results are seen when comparing Yamaguchi's assay results with Appellant's results.
  - This argument has been addressed above in the Office's rebuttal to the arguments in the Second Section B.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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